PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
95.85070		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB2004/003398	04.08.2004	04.08.2003

International Patent Classification (IPC) or national classification and IPC

B01J13/00, B01J13/02

Applicant

CAMURUS AB

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of two sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.06.2005	03.11.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003398

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-48	as originally filed
Claims, Numbers	
1-22	received on 04.07.2005 with letter of 01.07.2005
Drawings, Sheets	
1/5-5/5	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,4-10,13,15,17-19,21,22
	No:	Claims	1,3,11,12,14,16,20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2,4-10,13,15,17-19,21,22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

1. The remarks in the applicant's letter dated 01.07.05 are noted, but the IPEA considers Document D1 (US-A-5 531 925) to be very relevant.

2. Fragmentation process d) recited in D1 at column 10, line 6 to column 11, line 26 involves co-equilibration of starting material and an amphiphilic substance at an elevated temperature (37°C) - which is presumably attained through heating - followed by rapid cooling. The resultant particles must be regarded as amphiphilic, since an amphiphile substance is involved. Furthermore it is clearly indicated in D1 that bioactive agents can be present during this fragmentation - see column 18, lines 58-64, and that fragmentation is a process which results in loading of an active compound (column 8, lines 16-19). Claim 15 also indicates that a bioactive agent " is added at any stage of the preparation". Thus, the total disclosure of D1 is regarded as having made available, within the meaning of Rule 64.1(a) PCT, the subject-matter of present claims 1, 3, 11, 12, 14, 16, 20 - see also claims 17, 19 and 23 of D1.

3. Claims 1, 3, 11, 12, 14, 16 and 20 are not allowable under Article 33(2) PCT.

4. The additional subject-matter in present claims 2, 4-10, 13, 15, 17-19, 21, 22 does not appear to contribute towards increasing the level of active agent loading (cf. present description, page 7, first paragraph), since this has already been achieved though heating and cooling. No inventive step can be acknowledged for the said subject-matter.

5. Claims 2, 4-10, 13, 15, 17-19, 21, 22 are not allowable under Article 33(3) PCT.

Claims

1. A method for the production of amphiphile particles having incorporated therein at least one active agent, said method comprising forming a dispersion of particles comprising at least one amphiphilic structuring agent, followed heating said dispersion to an elevated temperature in a solution of at least one active agent, and then cooling to around ambient temperature.

2. A method as claimed in claim 1 wherein said heating is to a temperature and for a period sufficient to provide, after cooling, an incorporation of active agent into said particles which is at least 130% of the maximum incorporation provided by equilibrating said particles in a solution of at least one active agent at 37°C for up to 3 days.

3. A method as claimed in claim 1 or claim 2 wherein said particles are colloidal.

4. A method as claimed in any of claims 1 to 3 wherein said heating is to a temperature in the range 75°C to 200°C.

5. A method as claimed in any of claims 1 to 4 wherein said heating is for a period of between 1 minute and 4 hours.

6. A method as claimed in any of claims 1 to 5 wherein, prior to incorporation of said active agent, at least 75% by volume of said particles are of non-lamellar or micellar phase.

7. A method as claimed in any of claims 1 to 6 wherein, after incorporation of said active agent, at least 75% by volume of said particles are of non-lamellar or micellar phase.

8. A method as claimed in any of claims 1 to 7 wherein, before incorporation of said active agent, the equilibrium form of the particles is non-lamellar or micellar.

9. A method as claimed in any of claims 1 to 8 additionally comprising drying the amphiphile particles having incorporated therein at least one active agent.

10. Amphiphile particles comprising at least one structure forming amphiphile and an active agent, wherein the incorporation of said active agent into said particles is at least 130% of the maximum incorporation provided by incubating equivalent particles not comprising any active agent in a solution of an excess of said active agent at 37°C.

11. Amphiphile particles as claimed in claim 10, having incorporated therein at least one active agent, said particles being formed by the method of any of claims 1 to 10.

12. Amphiphile particles as claimed in claim 10 or claim 11 wherein said structure forming amphiphile is one or more amphiphiles selected from natural lipids, synthetic lipids, surfactants, and amphiphilic copolymers.

13. Amphiphile particles as claimed in any of claims 10 to 12 wherein a portion of said structure forming amphiphile is a fatty acid and/or an oily amphiphile.

14. Amphiphile particles as claimed in any of claims 10 to 13 wherein said particles are colloidal.

15. Amphiphile particles as claimed in any of claims 10 to 14 wherein the particles are at least 75% by volume non-lamellar or micellar particles or mixtures thereof.

16. Amphiphile particles as claimed in any of claims 10 to 15 additionally comprising at least one fragmenting agent.

17. Amphiphile particles as claimed in claim 16 wherein said fragmenting agent is a surfactant with a hydrophilic lipophilic balance of at least 12.

18. Amphiphile particles as claimed in any of claims 10 to 17 wherein said particles are stable to the loss of said active agent for at least 24 hours at 25°C.

19. Amphiphile particles as claimed in any of claims 10 to 18 wherein said particles are stable in terms of particle size for at least 24 hours at 25°C.

20. A pharmaceutical composition comprising amphiphile particles as claimed in any of claims 10 to 19 and at least one pharmaceutically tollerable carrier or excipient.

21. A powder comprising particles as claimed in any of claims 10 to 20, optionally with some or all of the water therein removed.

22. A gel of cream comprising particles as claimed in any of claims 10 to 21, optionally with some or all of the water therein removed.